REMARKS

Reconsideration is requested.

Claims 1-13, 15, 23-36, 38-39 and 41-56 have been canceled, without prejudice. Claims 14, 16-22, 37 and 40 are pending. Claims 57-69 have been added. Support for the amended claims may be found throughout the specification, as further described below. No new matter has been added. Upon entry of the present amendment, claims 14, 16-22, 37, 40 and 57-69 will be pending.

The applicants acknowledge, with appreciation, the Examiner interview of December 5, 2003. The Interview Summary is an a brief and accurate summary of the issues discussed during the interview.

The following is submitted in response to the clarification of the indicated items requested by the Examiners during the interview.

The constructs of the Examples of the present specification contain a sequence encoding the amino acids encoded by MGF exons 3/4/5/6, i.e. the amino acid sequence of Figure 5 or SEQ ID NO: 2. As noted on page 9 of the specification, Figures 6 and 7 (i.e., SEQ ID NOs: 4 and 6) also describe amino acid sequences of MGF exons 3/4/5/6. Thus, the sequence encoded by the construct is a preferred embodiment discussed at page 10, lines 4-5 of the specification. The Examiner is urged to appreciate however that the specification also describes that proteins of the invention include sequences having the 4-5-6 exon structure. See, page 9, lines 17-19 and page 11, lines 15-17, for example. The specification describes the present invention as including MGF, which is

any IGF-I splice variant that includes the characteristic 4-5-6 exon pattern as opposed to the 5/6 exon pattern of regular liver-type IGF-I. The claims have been amended to recite these two embodiments of the disclosed invention, without prejudice, to advance prosecution. The recited percent identities are described, for example, at page 12, lines 4-5 of the specification.

The specification has been amended above to include sequence identifiers for the sequences of the figures. Support for the amendments may be found throughout the specification. Specifically, page 9, lines 16-23 discloses that Figures 5, 6 and 7 describe SEQ ID NOs: 1-6 and that Figures 8, 9 and 10 describe SEQ ID NOs: 9-14. See, also page 10, lines 15-23 of the specification.

Moreover, one of ordinary skill in the art will appreciate from page 9 and the entirety of the specification that Figure 11 is a comparison of the amino acid sequences of human, rat and rabbit MGF and human, rat and rabbit IGF-1 and that Figure 11 describes exons 4-6, as compared to Figures 5-9 (i.e., SEQ ID NOs: 2, 4, 6 (MGF) and 9, 10, 12 and 14 (IGF-I)) which also describe Exon 3. In each sequence in Figure 11, the first amino acid is amino acid 26 (Asn) in the corresponding sequence in Figures 5-9 and SEQ ID NOs: 1-14. Figure 11 therefore describes the following: Hu MGF:Amino Acid No. 1 = Amino Acid No. 26 of SEQ ID NO: 2 and Figure 5; Rat MGF: Amino Acid No. 1 = Amino Acid No. 26 in SEQ ID NO: 4 and Figure 6; Rab MGF: Amino Acid No. 1 = Amino Acid No. 26 in SEQ ID NO: 6 and Figure 7; Hu IGF: Amino Acid No. 1 = Amino Acid No. 26 in SEQ ID NO:10 and Figure 8; Rat IGF: Amino Acid No. 1 = Amino Acid No. 26 in SEQ ID NO: 12 and Figure 9; Rab IGF: Amino Acid No. 1 = Amino Acid No.

26 in SEQ ID NO: 14 and Figure 10. The specification has been amended to include this specific disclosure.

As for the recitation of percent identity, the specification describes on page 12, for example, the recited values. Moreover, as requested by the Examiners during the interview, the applicants note the following with regard to the sequences of the Figures and their similarity.

There are fairly few differences between the human, rat and rabbit exon 3/4/5/6 MGF sequences, and similarly there are fairly few differences between the human, rat and rabbit exon 4/5/6 MGF sequences. However, the identity between some pairs of the three sequences is less than 90%, the lowest being for human/rat at 82.6% by the calculations further described below. The above recited 80% or greater and 90% or greater sequence identity therefore is believed to also be supported by the examples of the present specification.

The Examiner is requested to consider the following sequence alignment and discussion in this regard.

Sequence SEQ ID NO: 2 (Human, Figure 5) 3-4-5-6
Sequence SEQ ID NO: 4 (Rat, Figure 6) 3-4-5-6
Sequence SEQ ID NO: 6 (Rabbit, Figure 7) 3-4-5-6

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Hu  Gly Pro Glu Thr Leu Cys Gly Ala Glu Leu Val Asp Ala Leu Gln Phe
Rat Gly Pro Glu Thr Leu Cys Gly Ala Glu Leu Val Asp Ala Leu Gln Phe
Rab Gly Pro Glu Thr Leu Cys Gly Ala Glu Leu Val Asp Ala Leu Gln Phe
     1               5                  10                  15

                                                  Exons 4-6
Hu  Val Cys Gly Asp Arg Gly Phe Tyr Phe Asn Lys Pro Thr Gly Tyr Gly
Rat Val Cys Gly Pro Arg Gly Phe Tyr Phe Asn Lys Pro Thr Val Tyr Gly
Rab Val Cys Gly Asp Arg Gly Phe Tyr Phe Asn Lys Pro Thr Gly Tyr Gly
                20                  25                  30

Hu  Ser Ser Ser Arg Arg Ala Pro Gln Thr Gly Ile Val Asp Glu Cys Cys
Rat Ser Ser Ile Arg Arg Ala Pro Gln Thr Gly Ile Val Asp Glu Cys Cys
Rab Ser Ser Ser Arg Arg Ala Pro Gln Thr Gly Ile Val Asp Glu Cys Cys
                35                  40                  45

Hu  Phe Arg Ser Cys Asp Leu Arg Arg Leu Glu Met Tyr Cys Ala Pro Leu
Rat Phe Arg Ser Cys Asp Leu Arg Arg Leu Glu Met Tyr Cys Val Arg Cys
Rab Phe Arg Ser Cys Asp Leu Arg Arg Leu Glu Met Tyr Cys Ala Pro Leu
          50                  55                  60

Hu  Lys Pro Ala Lys Ser Ala Arg Ser Val Arg Ala Gln Arg His Thr Asp
Rat Lys Pro Thr Lys Ser Ala Arg Ser Ile Arg Ala Gln Arg His Thr Asp
Rab Lys Pro Ala Lys Ala Ala Arg Ser Val Arg Ala Gln Arg His Thr Asp
     65              70                  75                  80

Hu  Met Pro Lys Thr Gln Lys Tyr Gln Pro Pro Ser Thr Asn Lys Asn Thr
Rat Met Pro Lys Thr Gln Lys Ser Gln Pro Leu Ser Thr His Lys Lys Arg
Rab Met Pro Lys Thr Gln Lys Tyr Gln Pro Pro Ser Thr Asn Lys Lys Met
                85                  90                  95

Hu  Lys Ser Gln     Arg Arg Lys Gly Ser Thr Phe Glu Glu His Lys
Rat Lys Leu Gln Arg Arg Arg Lys Gly Ser Thr Leu Glu Glu His Lys
Rab Lys Ser Gln Arg Arg Arg Lys Gly Ser Thr Phe Glu Glu His Lys
                100                 105                 110
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Comparisons:

Exons 4-5-6

Human/Rat: 1-(15/86)= 82.6%
Human/Rabbit: 1-(4/86) = 95.4%
Rat/Rabbit: 1-(14/86)= 83.7%

Exons 3-4-5-6

Human/Rat: 1-(16/111)= 85.6%
Human/Rabbit: 1-(4/111) = 96.4%
Rat/Rabbit: 1-(15/111)= 86.5%

For exons 4-6, for example, the similarity can be seen graphically in the Figure 11 comparison. Specifically, SEQ ID NO: 2 (Human MGF) is 110 amino acids long, while SEQ ID NOs: 4 and 6 (Rat/Rabbit) have 111 amino acids. See, Figure 11 (final group of lines) for the location of the gap in human MGF. If, for example, these three sequences are lined up in the manner of Figure 11 but also including exon 3 in each case (cf. Figures 5-7), as a measure of sequence identity, there are the following 15 differences between human and rat: (i-ii) Gly/Val and Ser/Ile at Figure 11, first group of lines, positions 5 and 10, (iii-vii) Ala/Val, Pro/Arg, Leu/Cys, Ala/Thr and Val/Ile at Figure 11, second group of lines, positions 13-15, 18 and 24, (viii-xii) Tyr/Ser, Pro/Leu, Asn/His, Asn/Lys, Thr/Arg at Figure 11, third group of lines, positions 14, 17, 20, 22 and 23, (xiii) Ser/Leu at Figure 11, fourth group of lines, position 1, (xiv) Gap in Human MGF at Figure 11, fourth group of lines, position 3, and (xv) Phe/Leu at Figure 11, third group of lines, position 10. Moreover, there are the following four (4) differences between human and rabbit: (i) Ser/Ala at Figure 11, second group of lines, position 20, (ii-iii) Asn/Lys, Thr/Met at Figure 11, third group of lines, positions 22 and 23, and (iv) Gap in Human MGF at Figure 11, fourth group of lines, position 3. Finally, there are the following 14 differences between rat and rabbit: (i-ii) Val/Gly and Ile/Ser at Figure 11, first group of lines, position 10, (iii-viii) Val/Ala, Arg/Pro, Cys/Leu, Thr/Ala, Ser/Ala and Ile/Val at Figure 11, second group of lines, positions 13-15, 18, 20 and 24, (ix-xii) Ser/Tyr, Leu/Pro, His/Asn, Arg/Met at Figure 11, third group of lines, positions 14,

17, 20 and 23), (xiii) Leu/Ser at Figure 11, fourth group of lines, position 1, (xiv) Leu/Phe at Figure 11, fourth group of lines, position 10.

Accordingly, the sequence similarity or identity over the sequence of exons 4-6, as a measure of sequence similarity, is as follows: human/rat = 82.6% (i.e., 1 - 15/86); human/rabbit = 95.4% (i.e., 1 - 4/86) ; rat/rabbit = 83.7% (i.e., 1 - 14/86). The compared sequences of exons 4-6 of the specification have 86 amino acids, where the gap in the human sequence is being counted, in this example, as both a difference and a place-holder.

In exon 3, there is one (1) further difference between human and rat ((xvi) Compare Figure 5 (human), amino acid sequence position 20, Asp, with Figure 6 (rat), amino acid sequence position 20, Pro); no further differences between human and rabbit; and one (1) further difference between rat and rabbit ((xv) Compare Figure 6 (rat), amino acid sequence position 20, Pro with Figure 7 (rabbit), amino acid sequence position 20, Asp).

Thus, in the exon 3-6 sequences of SEQ ID NOs: 2, 4 and 6, there are a total of: 16 differences between human and rat; 4 differences between human and rabbit; and 15 differences between rat and rabbit. Taking the 111 amino acid length of the compared sequences across exons 3-6, this gives 16/111 x 100 = 14.4 % difference, or 85.6% identity between human and rat; 4/111 x 100 = 3.6% difference, or 96.4% identity between human and rabbit; and 15/111 x 100 = 13.2% difference, or 86.5% identity between rat and rabbit.

GOLDSPINK et al.
Serial No. 09/852,261
February 16, 2004

The claims are submitted to be supported by an enabling disclosure which adequately describes the claimed invention.

Reconsideration and withdrawal of the Section 112, first paragraph, rejection of claims 14-56 stated in ¶6 of the Office Action dated July 2, 2003 (Paper No. 18) is requested in view of the above and arguments of record.

The claims are submitted to be in condition for allowance and a Notice to that effect is requested.

The Examiner is invited to contact the undersigned in the event anything further is required to place the application in condition for allowance.

Respectfully submitted,

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